Remarks

Claims 1-10, 12-14 are pending. Claims 10, has been amended, applicants have cancelled claim 11. No new matter has been introduced into this application by way of amendment. In the paper dated 12/7/2005, applicants had requested rejoinder of method and process claims 10-12 of equal scope to compound claims upon a determination of allowable compound claims. In a telephone conversation with the examiner on July 20, 2006, the Examiner had requested journal article citations to support the enablement of method claim 10. These are submitted herein below.

The discussion in the Background section provides references which create the nexus between the activity possessed by the instant compounds and the claimed diseases. In addition, Applicants provide further evidence submitted herein below establishing a correlation between the presently claimed diseases and asserted activity in the specification. Several of the references below are also cited in the Background section. A summary of each is provided below.

Rheumatoid Arthritis, Crohn's disease. Early Alert Report, Fall 2000. This article reviews TNFα inhibitors, both biological and small molecule, and discusses their uses in the aforementioned diseases.

Inflammatory bowel diseases, Ulcerative Colitis: van Heel et al., *Human Molecular Genetics* (2002) discloses that IBD is characterized by increased levels of TNFα and that anti-TNF therapy is efficacious in treating the disease.

Osteoarthritis: A study by G.R. Webb et al., *Osteoarthritis and Cartilage*, 1997, 5, 427, showed that cartilage in explants from knee joints from osteoarthritic patients was more susceptible to degradation stimulated by TNFα than in explants from non-arthritic patients, suggesting a role for TNFα in osteoarthritis.

Multiple sclerosis: A role for TNFα in multiple sclerosis is suggested by the finding that levels of TNFα correlate with disease progression (C.S. Raine et al., *Rev. Neurol.* (Paris) 1998, 154, 577).

Guillain-Barre Syndrome: A study of genetic polymorphisms in patients with Guillain-Barre Syndrome showed higher frequency of an allele associated with high TNFα production suggesting a role for TNFα in that disease (J.J. Ma et al., *Annals of Neurology*, 1998, 44, 815).

Psoriasis: G. Chodorowska, *J. Eur. Acad. Dermatol. And Venesol.*, 1998, 10, 147, indicates that TNFα and INF-γ have important roles in the inflammatory process of psoriasis.

Graft-versus-host disease (GVHD): in a study of patients who have undegone allogenic bone marrow transplantation, A. Nagler et al., *Cytokines, Cellular & Molecular Ther.*, 1998, 4, 161, found a positive correlation between elevated TNFα levels and development of GVHD. They also mentioned that an anti-TNFα antibody has shown encouraging results in preventing GVHD.

Systemic lupus erythematosus (SLE): in a study of patients with SLE, E. Robak found that levels of TNFα were elevated in SLE patients compared to normal controls and also that there was a correlation between levels of TNFα and disease activity. Robak, E. *Archivum Immunologiae et Therapiae Experimentalis*, 1998, 46,375-380.

Restenosis after Percutaneous transluminal coronary angioplasty (PCTA): a patient study discussed in the paper indicates that proinflammatory cytokines, six including TNFα, are associated with restenosis after PCTA. Tashiro, H. et al. *Coronary Artery Disease*, 12:107-113.

Diabetes: TNFα has been reported to play a key role in insulin resistance leading to type II diabetes (P. Storz et al., *FEBS Letters*, 1998, 440, 41). Inhibition of TNFα has been shown

to be protective against Type I diabetes in non-obese diabetic mice as well (G.R. Brown et. al., *Diabetologia*, 1998, 41, 1502).

Toxic shock syndrome and sepsis: in a study with mouse monocytes and lymphocytes, treatment of these cells with an immunomodulator suppressed formation of TNFα upon stimulation of these cells with toxic shock syndrome toxin 1 (J. Soltys and M.T. Quinn, *Infection and Immunity*, 1999, 244). The authors suggest that treatment with agents that reduce levels of proinflammatory cytokines such as TNFα can be beneficial in toxic shock syndrome and sepsis.

Alzheimer's disease: K.B. Bjugstad et al., *Brain Research*, 1998, 795, 349, reported that in patients with AIDS dementia complex levels of TNFα are consistently elevated. They also report that enhanced levels of TNFα have been found in the brains of patients with Alzheimer's disease and suggest that the inflammation brought about by TNFα may be responsible for damage in these neurodegenerative diseases.

Chronic neuropathic pain: R.C. Chou et al., *J. Neuroimmunol.*, 1998, 82, 140, report that release of TNFα, regulated by an adrenergic mechanism contributes to the pathogenesis of several models of chronic neuropathic pain.

Contact Dermatitis: a review article discusses studies which indicate that allergic contact dermatitis and irritant contact dermatitis are characterized by different cytokine patterns which seem to be highly specific. Muller, G. *American Journal of Contact Dermitis*. Vol 7, No.3 (September), 1996: pp 177-184.

Atherosclerosis : A study suggests a crucial role for TNF in females and IL-1 in both sexes during the initial step of the atherosclerotic process of a mouse model. Elhage, R. *Circulation*. 1998; 97:242:244.

Glomerulonephritis: using TNFα deficient mice and a model of glomerulonephritis, B. Ryffel et al., *Int. J. Exp. Path.*, 1998, 79, 453, found that TNFα plays a key role in recruitment of inflammatory cells and subsequent development of glomerulonephritis.

Reperfusion injury:

Nerve Injury: a study by Mitsui, Y. et al. *Brain Research* 844 (1999) 192-195, supports the notion that TNFα and IL-1beta are involved in the inflammatory response of ischemia-reperfusion injury to the peripheral nervous system.

Renal ischemia: a study focusing on (MIP)-2, mentions that IL-1beta, and to a lesser extent TNFα, were expressed in a murine model of ischemia-reperfusion injury. Lemay. S. et al. *Transplantation*, Vol 69, 959-963, No. 5, March 15, 2000.

Intestinal ischemia-reperfusion injury: Intestinal I/R injury is commonly associated with injury to remote organs from the initial site. Borjession, A. et al. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 278:L3-L12, 2000, reports that injury to the lungs after intestinal injury may be due in-part to TNFα.

Osteoporosis: A report by K. Kurokouchi et al., *J. Bone and Mineral Res.*, 1998, 13, 1290., suggests that TNFα plays an important role in the production of cytokines and cell adhesion molecules in osteoblasts leading to bone resorption and inflammation in osteoporosis.

Chronic Obstructive Pulmonary Disease (COPD): the major cause COPD is smoking. Less common are genetic factors which contribute to COPD. Certain genetic factors were studied by Higham et al. *Eur Respir J 2000*; 15:281-284 which concluded that while an association between the TNF2 allele and an increases risk of developing COPD was established in a male Taiwanese population, such a correlation was not demonstrated in a Caucasian population of smokers. Takabatake, N. et al. *Am J Respir Crit Care Med.* Vol 161 pp 1179-1184, 2000, obtained data suggesting that systemic hypoxemia noted in patients with COPD is associated with activation of the TNFα system *in vivo*.

Asthma: in vivo studies suggest evidence for cytokine involvement in asthma, these cytokines include GM-CSF, IL-3, IL-4,IL-5, IL-6 and TNFα. Lee, TH. *Journal of the Royal College of Physicians of London*. Vol 32 No.1, Jan/Feb 1998, pp56-64.

Stroke: J.M. Lipton et al., *Neuroimmunomodulation*. 1998, 5, 178, report that TNFα contributes to the inflammatory processes responsible for neurodegenerative diseases including stroke.

Myocardial infarction (MI): a study by D. Li et al., *Amer. Heart Journal*, 1999, 137, 1145, found TNFα levels increased in patients with myocardial infarction (MI). In a further study with a rabbit model of MI, a TNFα antibody reduced the size of necrosis. The study suggests that TNFα contributes to myocardial injury and treatment with an agent that inhibits TNFα can be cardioprotective in MI.

Thermal injury: in a study of burn patients (F.L. Yeh et al., *Burns*, 1997, 23, 6) TNFα levels were found to be elevated, with highest levels in patients who did not survive. The authors suggest that inhibition of exaggerated production of TNFα would be beneficial in treatment of thermal injury.

Adult respiratory distress syndrome (ARDS): a study in guinea pigs and rats (L.M. Renzetti and P.R. Gater, *Inflamm. Res.* 1997, 46, Suppl. 2, S143) suggested that compounds that inhibit TNFα may be useful in treating a number of pulmonary diseases including ARDS.

Multiple organ injury: in a study with rats S. Bahrami et al., *Am. J. Physiol*, 1997, 272 (*Heart Circ. Physiol*. 41), H2219, suggested that TNFα is an important mediator in multiple organ injury following a traumatic insult (hemorrhagic shock), the paper indicates that treatment with inhibitors such as monoclonal antibodies to TNFα would be beneficial.

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Dermatoses: F. Ameglio et al., *J. Biol. Regul. Homeost. Agents*, 1997, 11, 148, found that TNFα serum levels were increased in dermatoses including bullous pemphigoid and pemphigus vulgaris, and levels correlated with the number of lesions.

Meningitis: in a rabbit model of meningitis, M.M. Paris et al., *J. Infectious Dis*., 1997, 176, 1239, showed that the anti-inflammatory cytokine IL-10 reduced the level of TNFα in the cerebrospinal fluid. The authors suggest that agents that can do this may be beneficial in modulation, the inflammatory response in meningitis.

Necrotizing enterocolitis: R.M. Viscardi et al., *Pediatric Pathol. And Lab. Medicine*, 1997, 17, 547, found higher level of mRNA for TNFα in intestinal sections of infants with necrotizing enterocolitis, suggesting that it is one of the inflammatory cytokines involved in augmentation of the inflammatory response in this disease.

In view of the foregoing, allowance of all pending claims is respectfully requested.

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